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<p>(21) International Application Number: PCT/US92/02699</p> <p>(22) International Filing Date: 3 April 1992 (03.04.92)</p> <p>(30) Priority data: 680,201 4 April 1991 (04.04.91) US</p> <p>(71) Applicant: THE CHILDREN'S MEDICAL CENTER CORPORATION [US/US]; 55 Shattuck Street, Boston, MA 02115 (US).</p> <p>(72) Inventor: LIPTON, Stuart, A. ; 58 Ober Road, Newton, MA 02159 (US).</p> <p>(74) Agent: FREEMAN, John, W.; Fish & Richardson, 225 Franklin Street, Boston, MA 02110-2804 (US).</p>		<p>(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent).</p> <p>Published <i>With international search report.</i></p>	
<p>(54) Title: METHOD OF PREVENTING NMDA RECEPTOR-MEDIATED NEURONAL DAMAGE</p> <p>(57) Abstract</p> <p>Disclosed is a medicament for administration to a mammal to reduce NMDA receptor-mediated neuronal damage; the medicament comprises a compound of the formula shown in Fig. 1, wherein R₁ includes an amino group and R₂-R₁₇ are independently H or a short chain aliphatic group comprising 1-5 carbons, or a physiologically-acceptable salt thereof, in a concentration effective to cause such reduction.</p>			

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METHOD OF PREVENTING NMDA RECEPTOR-MEDIATED NEURONAL DAMAGE

Background of the Invention

This invention relates to the treatment of nervous system disorders, particularly disorders mediated by the N-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptor.

Glutamate has been implicated as a significant factor in the neurotoxicity associated with hypoxic-ischemic encephalopathy, seizures, trauma, and several degenerative neurological disorders such as the AIDS dementia complex and other neurological manifestations of AIDS, Huntington's disease and Parkinsonism (Hahn et al., *Proc. Natl. Acad. Sci. USA* 85:6556, 1988; Choi, *Neuron* 1:623, 1988; Rothman et al., *Trends Neurosci.* 10:299, 1987; Meldrum et al., *Trends Pharm. Sci.* 11:379, 1990). In many central neurons the predominant form of this neurotoxicity appears to be mediated by activation of the NMDA subtype of glutamate receptor and subsequent influx of excessive Ca^{2+} (Choi, *ibid*; Weiss et al., *Science* 247:1474, 1990).

Turski et al. (*Nature* 349:414, 1991), which is not admitted to be prior art, reports that certain NMDA antagonists protect against neurotoxicity involved in specific etiologies of Parkinsonism. Braunwald et al. (*Principles of Internal Medicine*, 11th ed., p. 2017, New York, McGraw Hill, 1987) report that amantadine has been used to treat Parkinson's disease and that its effect is achieved by its capacity to release stored dopamine from presynaptic terminals.

Summary of the Invention

In general, the invention features a method for reducing NMDA receptor-mediated neuronal damage in a

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mammal. The method involves administering to the mammal a compound of the formula shown in Fig. 1, wherein R₁ includes an amino group, and R₂-R₁₇, are independently H or a short chain aliphatic group including 1-5 carbons, or a 5 physiologically acceptable salt thereof, in a concentration effective to cause such reduction.

In preferred embodiments, R₁ is NH₂, and the compound is preferably amantadine; R₄ is a methyl group; R₁₀ is a methyl group; R₄ and R₁₀ are both methyl groups; 10 R₄ and R₁₀ are both methyl groups and R₁ is NH₂, and the compound is preferably memantine.

Alternatively, R₁ may be



wherein X₁ and X₂ are independently H or a short chain aliphatic group including between 1-5 carbons [i.e., either a methyl group or between 1-4 (-CH₂) groups and a terminal methyl group]; R₄ is a methyl group; R₁₀ is a 20 methyl group; R₄ and R₁₀ are methyl groups; X₁ and X₂ are H and CH₃, respectively, or X₁ and X₂ are CH₃ and H, respectively; and the compound is preferably rimantadine.

In various other preferred embodiments, the mammal is a human infected with a human immune deficiency virus; 25 the human manifests symptoms of the AIDS related complex or acquired immune deficiency syndrome; the neurotoxicity is mediated by an excitatory amino acid; and the neurotoxicity is mediated by glutamate, aspartate, homocysteic acid, cysteine sulphonic acid, cysteic acid, 30 quinolinate, or N-acetyl aspartyl glutamate.

By "NMDA receptor-mediated neuronal damage" is meant any neuronal injury which resulting from stimulation or costimulation of the NMDA receptor.

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By "excitatory amino acid" is meant any amino acid which leads to the activation of an NMDA receptor-operated ionic channel.

Useful compounds of the instant invention include 5 a tricyclic 10 carbon ring which includes at least one amino group at position R₁ of the general formula shown in Fig. 1. The amino group may be attached directly to a ring carbon (as is the case for amantadine; see Fig. 2a), or it may be attached to a carbon attached to the carbon 10 ring (as is the case for rimantadine; see Fig. 2b). R₂-R₁₇ (of the general formula of Fig. 1) are hydrogen atoms, methyl groups, or short chain aliphatic groups which include between 1-5 saturated carbons [i.e., 1-4 (-CH₂) groups and a terminal methyl group], or any combination, 15 thereof. The neuroprotective potency of the compounds may be enhanced by substitutions of ring hydrogens. In one example, methyl group substituants at positions R₄ and R₁₀ (of the general formula shown in Fig. 1) greatly enhance the ability and potency of the compound, 20 memantine (shown in Fig. 2c), to prevent glutamate-induced neuronal damage. Memantine is neuroprotective in vitro at a concentration of 6μM (see below); amantadine, a molecule unsubstituted at these positions, is effective at a concentration of approximately 200μM. The water 25 solubility of compounds of the general formula shown in Fig. 1 may be increased by formulating the compound into a physiologically-acceptable salt, e.g., by reaction with HCl.

The preferred compounds of the invention (i.e., 30 amantadine, rimantadine, and memantine, and similar derivatives) are water soluble and are able to pass readily through the blood brain barrier, facilitating a therapy which is both extremely rapid and unusually potent. The preferred compounds also provide the 35 advantage of a proven record of safe human administration

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(i.e., for treatment of viral infections or for treatment of Parkinson's disease, but not neuronal degeneration of Parkinsonism). For example, amantadine has been approved for use by human patients, at least, in the United States. Disorders which may be treated by the method of the invention include hypoxia-ischemic encephalopathy, seizures, stroke, AIDS dementia and other neurological manifestations of AIDS (see, e.g., USSN 571,949) and, generally, acute and chronic neurodegenerative disorders.

Other features and advantages of the invention will be apparent from the following detailed description and from the claims.

Detailed Description

The drawings are first briefly described.

Drawings

Fig. 1 is the general formula of the compounds useful in the method of the invention.

Fig. 2 is a schematic representation of (a) amantadine, (b) rimantadine, and (c) memantine.

Fig. 3 is a graphical representation showing that memantine prevents glutamate-mediated retinal ganglion cell neurotoxicity.

The present invention is based on the finding that the amantadine derivative memantine (1-amino-3,5-dimethyl adamantine) reduces neuronal damage (see below); and that this reduction in damage is due to a block of NMDA receptor-operated channel activation by excitatory amino acids (such as glutamate-related compounds) using concentrations of memantine that are readily obtainable in human patients taking the drug (Wesemann et al., *J. Neural Transmission (Supp.)* 16:143, 1980). An increased level of one or more glutamate-related compounds is associated with many neurodegenerative disorders (e.g., those listed above), and amantadine derivatives are therefore useful for their treatment. In addition to

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glutamate itself, neuronal injury may result from stimulation of the NMDA receptor by other excitatory amino acids, such as aspartate, homocysteic acid, cysteine sulphenic acid, or cysteic acid, or from 5 stimulation by excitatory peptides, such as N-acetyl aspartyl glutamate.

Other compounds structurally related to memantine are also preferred for use in the invention. By "structurally related" is meant a compound composed of a 10 tricyclic 10 carbon ring bearing an amino group. Such compounds include, but are not limited to, amantadine (1-adamantanamine hydrochloride) itself and rimantadine (alpha-methyl-1-adamantanemethylamine hydrochloride).

Compounds of the invention (i.e., those of the 15 general formula shown in Fig. 1 and including compounds bearing substitutions predicted to increase potency) may be tested for efficacy in reducing neuronal damage using the assay described below; an effective compound will cause a decrease in neuronal cell death. Compounds most 20 preferred in the invention are those which effect the greatest protection of neurons from NMDA receptor-mediated injury, e.g., that injury resulting from stimulation of the NMDA receptor by glutamate (as shown below) or other excitatory amino acids or stimulation by 25 excitatory peptides, such as N-acetyl aspartyl glutamate.

Assay for Neuronal Cell Function and Death

To test amantadine derivatives for their ability to prevent neurotoxicity, neuronal cell death may be assayed as follows. Under general anesthesia, the 30 fluorescent dye granular blue (Mackromolecular Chemin, Umstadt, FRG) is injected as approximately a 2% (w/v) suspension in saline into the superior colliculus of 4-to 6-day-old Long-Evans rats (Charles River Laboratory, Wilmington, MA). Two to 6 days later, the animals are 35 sacrificed by decapitation and enucleated, and the

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retinas quickly removed. The retinas are dissociated by mild treatment with the enzyme papain and cultured in Eagle's minimum essential medium (MEM, catalog #1090, Gibco, Grand Island, NY) supplemented with 0.7% (w/v) 5 methylcellulose, 0.3% (w/v) glucose, 2mM glutamine, 1 µg/ml gentamicin, and 5% (v/v) rat serum, as described in Lipton et al., *J. Physiol.* 385:361, 1987. The cells are plated onto 75 mm² glass coverslips coated with poly-L-lysine in 35 mm tissue culture dishes. The candidate 10 amantadine derivative is added (e.g., in a series of concentrations ranging from 1nM - 1mM) in the presence or absence of compounds which activate the NMDA receptor-operated channel complex, and in high calcium, low magnesium medium (10mM CaCl₂, 50µM MgCl₂) to enhance NMDA- 15 receptor neuotoxicity in this preparation (Hahn et al., *Proc. Natl. Acad. Sci. USA* 85:6556, 1988; Levy et al., *Neurology* 40:852, 1990; Levy et al., *Neurosci. Lett.* 110:291, 1990). The degree of survival is compared to that in normal medium (1.8mM CaCl₂, 0.8mM MgCl₂), which 20 minimizes NMDA receptor-mediated injury in this preparation (Hahn et al., cited above). Incubations last 16-24 h at 37°C in an atmosphere of 5% CO₂/95% air. The ability of retinal ganglion cells to take up and cleave fluorescein diacetate to fluorescein is used as an index 25 of their viability as described in detail in Hahn et al. (*Proc. Natl. Acad. Sci. USA* 85:6556, 1988). Dye uptake and cleavage generally correlate well with normal electrophysiological properties assayed with patch electrodes.

30 To perform the viability test, the cell-culture medium is exchanged for physiological saline containing 0.0005% fluorescein diacetate for 15-45 s, and then cells are rinsed in saline. Retinal ganglion cell neurons that do not contain the fluorescein dye (and thus are not 35 living) often remain visible under both phase-contrast

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and UV fluorescence optics, the latter because of the continued presence of the marker dye granular blue; other dead retinal ganglion cells disintegrate, leaving only cell debris. In contrast, the viable retinal ganglion 5 cells display not only a blue color in the UV light but also a yellow-green fluorescence with filters appropriate for fluorescein. Thus, the use of two exchangeable fluorescence filter sets permits the rapid determination of viable ganglion cells in the cultures. The ganglion 10 cells are often found as solitary neurons as well as neurons lying among other cells in small clusters.

An amantadine derivative may be tested for utility in the method of the invention using any type of neuronal cell from the central nervous system, as long as the cell 15 can be isolated intact by conventional techniques. Although retinal cultures are used above, hippocampal cortex neurons or any neuron containing NMDA receptors (e.g., neurons from other regions of the cortex) may also be used. Such neurons may be prenatal or postnatal. In 20 one example, retinal cultures can be produced from postnatal mammals; they are well-characterized and contain a central neuron, the retinal ganglion cell, that can be unequivocally identified with fluorescent labels. A substantial portion of retinal ganglion cells in 25 culture display both functional synaptic activity and bear many, if not all, of the neurotransmitter receptors found in the intact retina.

There now follows an example of an amantadine derivative useful in the method of the invention and an 30 illustration of its efficacy in reducing neuronal damage. This example is provided to illustrate the invention and should not be construed as limiting.

Memantine Prevents NMDA Receptor-Mediated Neurotoxicity

Using the assay described above, the amantadine 35 derivative, memantine, was tested for its ability to

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increase survival of glutamate-treated retinal ganglion cells. In eight separate experiments, retinal ganglion cells were cultured in either normal medium (i.e., MEM containing 1.8mM CaCl₂, 0.8mM MgCl₂) or in high calcium, 5 low magnesium medium (i.e., 10mM CaCl₂, 50μM MgCl₂). The latter medium is known to enhance NMDA receptor-mediated neurotoxicity due to an endogenous glutamate receptor agonist (Hahn et al., *Proc. Natl. Acad. Sci. USA* 85:6556, 1988; Levy et al., *Neurology* 40:852, 1990; Levy et al., 10 *Neurosci. Lett.* 110:291, 1990). Memantine HCl was diluted in double-distilled water, filtered, and added to the growth media (to a final concentration of between 1μM - 25μM). The retinal cells were incubated for 16-20 hours at 37°C in a humidified atmosphere of 5% CO₂ and 15 95% air.

As shown in Fig. 3, an endogenous glutamate-like agonist produces retinal cell neurotoxicity in the presence of elevated extracellular calcium concentrations (compare Fig. 3, columns 1 and 2). To verify that the 20 agonist was glutamate-related, the enzyme glutamate-pyruvate transaminase (GPT; 0.25 mg/ml; Boehringer-Mannheim, Indianapolis, IN) was added; this enzyme specifically degrades endogenous glutamate by transaminating it to α-keto-glutarate in the presence of 25 pyruvate. Under these conditions, survival of retinal ganglion cells was enhanced; i.e., an approximately equal number of neurons survived in the high calcium, low magnesium medium plus GPT and pyruvate (2mM) as survived in the control cultures in normal medium. This finding 30 indicated that the endogenous toxin was glutamate itself. HPLC analysis verified the breakdown of glutamate by GPT.

The amantadine derivative, memantine, prevented retinal ganglion cell death from the endogenous glutamate-related toxin in a dose-dependent manner (Fig. 35 3). Increased neuronal survival at 6μM memantine (Fig.

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3, column 4) reached statistical significance compared to the control (Fig. 3, column 1). Doses of 25 μ M memantine or greater may themselves be toxic in retinal cell preparations under these conditions. All experiments 5 depicted in Fig. 3 involving memantine treatment were repeated in triplicate and normalized to control cultures (i.e., normal medium lacking memantine). The values depicted represent mean + standard error of the mean (SEM). An analysis of variance was used to test for 10 significance; this analysis was followed by a Sheffé test for multiple comparison of means (Hahn et al., 1988, supra).

These data indicate that memantine blocks neuronal cell death mediated by excessive stimulation of the NMDA 15 receptor. Without being bound to any theory as to the mechanism whereby memantine exerts its neuroprotective effect, it is possible that memantine blocks the glutamate-induced increase in intracellular Ca²⁺ at the NMDA receptor-associated ionic channel. By analogy with 20 MK-801 (dizocilpine; an NMDA-specific antagonist), the mode of action of memantine may be a non-competitive inhibition of Ca²⁺ influx by blocking the NMDA receptor-operated channels. If so, inhibition by memantine is contingent upon prior activation of the receptor by the 25 agonist. This has important consequences at the therapeutic level. Normal NMDA receptor activation (for example, that involved in the long-term potentiation stage of learning and memory) may be unaffected by the compounds of the invention while neuronal injury resulting from escalated glutamate levels following a 30 stroke or trauma to the central nervous system might be effectively blocked (Karschin et al., *J. Neurosci.* 8:2895, 1988; Levy and Lipton, *Neurology* 40:852, 1990). Memantine analogs have undergone clinical trials in the 35 United States and in the Soviet Union using therapeutic

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doses for influenza A therapy. Those studies revealed only limited and reversible central nervous system side effects (Tominack et al., *Infect. Dis. Clin. N. Am.* 1: (2):459, 1987; Clover et al., *Am. J. Dis. Child.* 140:706, 5 1986; Hall et al., *Pediatrics* 80(2):275, 1987; Zlydnikov et al., *Reviews of Infect. Dis.* 3(3):408, 1981; Dolin et al., *New Eng. J. Med.* 302:580, 1982). There has been one case report of visual loss in an adult patient who had been treated for Parkinson's symptoms with amantadine for 10 several weeks. However, full visual acuity returned after drug discontinuation (Perlman et al., *JAMA* 237:1200, 1977).

Therapy

To prevent neuronal damage, amantadine and its 15 derivatives may be administered by any of a number of routes in an amount sufficient to block glutamate's effect on the NMDA receptor. The amantadine derivative may be included in a pharmaceutical preparation, using a pharmaceutical carrier (e.g., physiological saline); the 20 exact formulation of the therapeutic mixture depends upon the route of administration. Preferably, the compound is administered orally or intravenously, but it may also be administered intrathecally or intravitrally. The preferred compounds, amantadine, memantine, and 25 rimantadine are administered at 100-500 µg/day, 5-80 mg/day, and 50-300 mg/day, respectively, in divided doses. Any other compound, determined to be an effective neuroprotective agent by the assays described herein, is administered orally, intravenously, intrathecally, or 30 intravitrally at 100µg-500 mg/day in divided doses. Treatment may be repeated as necessary to prevent or alleviate neurological injury. The compounds of the invention can be utilized to protect against a number of neurotoxic disorders caused by elevated levels of 35 glutamate or related compounds. Such neurotoxic

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disorders include ischemia, hypoxia, hypoglycemia, epilepsy, Huntington's disease, and Alzheimer's disease and other neurodegenerative disorders. The method of the invention is particularly preferred for the treatment of 5 AIDS dementia and other neurological manifestations of the AIDS virus. The method may also be used for reduction of neuronal damage resulting from infection with other viruses which cause damage to the nervous system.

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Other Embodiments

The method described herein is useful for reducing neuronal injury in any mammal having NMDA receptors. Treatment of neuronal damage in humans is the preferred utility; but the method may also be employed successfully 15 for veterinary purposes.

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Claims

1 1. A medicament for administration to a mammal
2 to reduce NMDA receptor-mediated neuronal damage in said
3 mammal, said medicament comprising a compound of the
4 formula shown in Fig. 1, wherein R₁ comprises an amino
5 group; and R₂-R₁₇ are independently H or a short chain
6 aliphatic group comprising 1-5 carbons, or a
7 physiologically acceptable salt thereof, in a
8 concentration effective to cause such reduction.

1 2. The medicament of claim 1, wherein R₁ is NH₂.

1 3. The medicament of claim 2, wherein said
2 compound is amantadine.

1 4. The medicament of claims 1 or 2, wherein R₄ is
2 a methyl group.

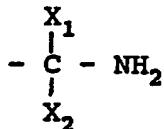
1 5. The medicament of claims 1 or 2, wherein R₁₀
2 is a methyl group.

1 6. The medicament of claim 1, wherein said R₄ and
2 R₁₀ are methyl groups.

1 7. The medicament of claim 6, wherein said R₁ is
2 NH₂.

1 8. The medicament of claim 7, wherein said
2 compound is memantine.

1 9. The medicament of claim 1, wherein R₁ is



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5 wherein X_1 and X_2 are independently H or a short chain
6 aliphatic group comprising between 1-5 carbons.

1 10. The medicament of claim 9, wherein X_1 and X_2
2 are H and CH_3 , respectively, or wherein X_1 and X_2 are CH_3
3 and H, respectively.

1 11. The medicament of claim 10, wherein said
2 compound is rimantadine.

1 12. The medicament of claim 9, wherein R_4 is a
2 methyl group.

1 13. The medicament of claim 9, wherein R_{10} is a
2 methyl group.

1 14. The medicament of claim 9, wherein R_4 and R_{10}
2 are methyl groups.

1 15. The medicament of claim 1, wherein said
2 mammal is a human infected with a human immune deficiency
3 virus.

1 16. The medicament of claim 15, wherein said
2 human manifests symptoms of the AIDS related complex or
3 acquired immune deficiency syndrome.

1 17. The medicament of claim 1, wherein said
2 neurotoxicity is mediated by an excitatory amino acid.

1 18. The medicament of claim 1, wherein said
2 neurotoxicity is mediated by glutamate, aspartate,
3 homocysteic acid, cysteine sulphonic acid, cysteic acid,
4 quinolinate, or N-acetyl aspartyl glutamate.

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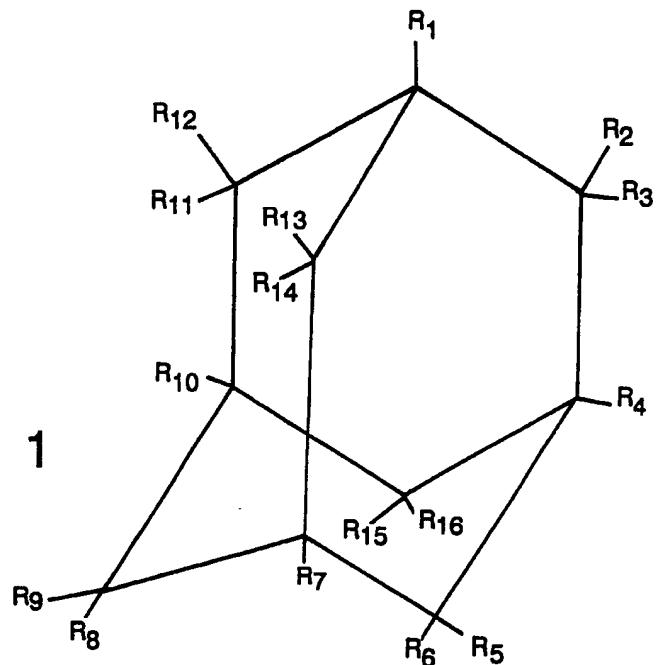


FIG. 1

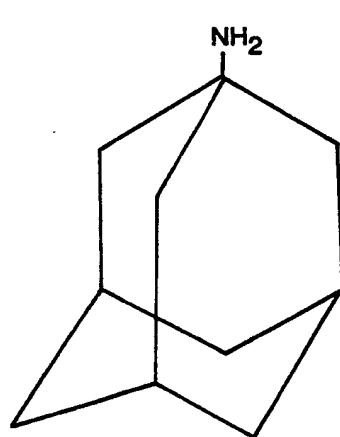


FIG. 2a

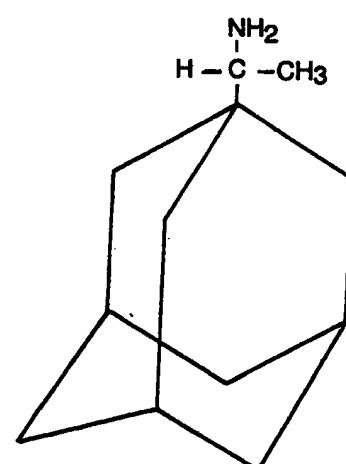


FIG. 2b

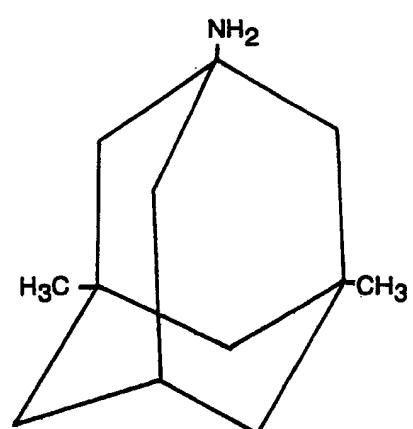


FIG. 2c

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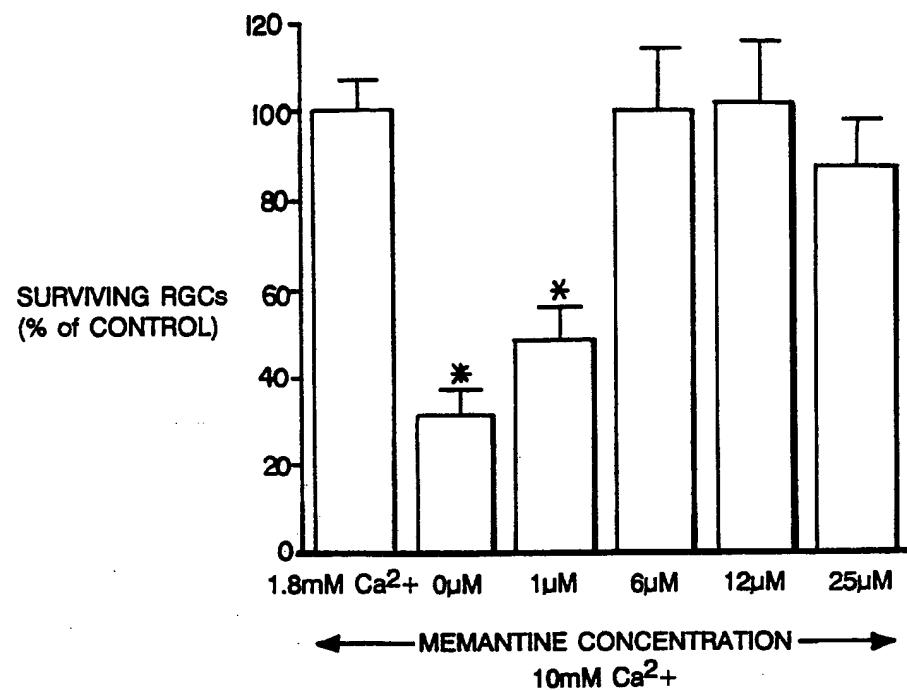


FIG. 3

SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/02699

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC(5): A61K, 31/13 U.S. Cl: 514/659		
II. FIELDS SEARCHED		
Minimum Documentation Searched ?		
Classification System	Classification Symbols	
U.S. Cl.	514/659, 662	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
Structure; neuronal damage, ischemia,		
III. DOCUMENTS CONSIDERED TO BE RELEVANT *		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages ***	Relevant to Claim No. *
Y,P	US, A, 5,061,703 (BORMANN ET AL) 29 October 1991, See entire document.	1-18
Y	US, A, 4,351,847 (GRIFFITH ET AL) 28 September 1982, See entire document.	1-18
Y	US, A, 4,122,193 (SCHERM ET AL) 24 October 1978, See entire document.	1-18
Y	US, A, 3,328,251 (SMITH) 27 June 1967, See entire document.	1-18
Y	<u>The Merck Index</u> , 10ed, 1985, no. A7, 373 and 8116.	1-18
* Special categories of cited documents: ** "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed *** "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu- ments, such combination being obvious to a person skilled in the art. "A" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 10 June 1992	Date of Mailing of this International Search Report 26 JUN 1992	
International Searching Authority ISA/US	Signature of Authorized Officer <i>Russell Travers</i>	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET**V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹**

This international search report has not been established in respect of certain claims under Article 17(2) (e) for the following reasons:

1. Claim numbers because they relate to subject matter¹³ not required to be searched by this Authority, namely:

2. Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out¹³, specifically:

3. Claim numbers because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.

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